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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/716,842
Filing Date: November 17, 2000
Appellant(s): BRIESEWITZ ET AL.

Edward J Baba
For Appellant

EXAMINER'S ANSWER

This is in response to the brief on appeal filed 6/23/06.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Ground of Rejection to be Reviewed on Appeal

The appellants' statement of the issues in the brief is substantially correct. The change is as follows: The enablement rejection has been withdrawn in view of Appellants' argument.

The issue on appeal is as follow:

Claims 16-18, 22-26, 30-34, 36, 40-44, 46-50 and 52-56 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Forsgren et al (of record, Cancer Res 39(12): 5155-64, Dec 1979; PTO 892) in view of WO 95/02684 (of record, Jan 1995; PTO 1449).

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

The following is a listing of the evidence (e.g., patents, publications, Official Notice, and admitted prior art) relied upon in the rejection of claims under appeal.

1. Forsgren et al, Cancer Res 39(12): 5155-64, Dec 1979; PTO 892.
2. WO 95/02684 publication (Jan 1995; PTO 1449).

(9) Grounds of Rejection

The following ground of rejection is applicable to the appealed claims:

Claim Rejection - 35 USC § 103 (a)

Claims 16-18, 22-26, 30-34, 36, 40-44, 46-50 and 52-56 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Forsgren et al (of record, Cancer Res 39(12): 5155-64, Dec 1979; PTO 892) in view of WO 95/02684 (of record, Jan 1995; PTO 1449).

Forsgren et al teach a method of targeting a drug to an intracellular site of a mammalian host such as male rat or patient with prostate carcinoma wherein the method comprises administering to the rat a bifunctional molecule such as Estracyt which consisting of a drug moiety such as nitrogen mustard linked to a targeting moiety such as estradiol-17 beta phosphate wherein said targeting moiety has affinity for its intracellular biodistribution modulating protein such as soluble estramustine in the ventral prostate (see abstract, page 5158, col. 1, page 5161, col. 2, in particular). The reference targeting protein binds to intracellular biodistribution modulating protein with high affinity such as 10 to 30 x 10^{-9} M which is "at least" 10^{-4} M (see abstract, page 5161, col. 1, in particular). Upon administration of the reference bifunctional molecule, the reference bifunctional molecule exhibits a modulate biodistribution to the ventral prostate gland (see abstract, in particular).

The claimed invention in claims 16 and 30 differs from the teachings of the reference only in that the method wherein the targeting moiety is a peptidyl-prolyl isomerase ligand instead of estradiol-17 beta phosphate and the bifunctional molecule having a molecule weight that does not exceed about 5000 daltons consisting of a drug moiety optionally joined by a linking group to peptidyl-prolyl isomerase ligand as the targeting moiety.

The claimed invention in claim 22 differs from the teachings of the reference only in that the method wherein the bifunctional molecule comprises a linking group.

The claimed invention in claims 40, 46 and 52 differs from the teachings of the reference only in that the method wherein the targeting moiety peptidyl-prolyl isomerase ligand is a ligand for an FKBP or cyclophilin.

The claimed invention in claims 41, 47 and 53 differs from the teachings of the reference only in that the method wherein the targeting moiety peptidyl-prolyl isomerase ligand is a ligand for an FKBP.

The claimed invention in claims 42, 48 and 54 differs from the teachings of the reference only in that the method wherein the targeting moiety peptidyl-prolyl isomerase ligand is a ligand for an FKBP selected from the group consisting of FK506 and rapamycin.

The claimed invention in claims 43, 49 and 55 differs from the teachings of the reference only in that the method wherein the targeting moiety is a ligand for cyclophilin.

The claimed invention in claims 44, 50 and 56 differs from the teachings of the reference only in that the method wherein the ligand for cyclophilin is a cyclosporine as the targeting moiety.

The WO 95/02684 publication teaches various binding pairs such as peptidyl-prolyl isomerase ligand FK506, FK520, rapamycin and derivative thereof that bind with an intracellular FKBP receptor, and cyclosporine that binds to cyclophilin receptor for targeting gene (see page 33, lines 25-27, page 36, lines 1-10, page 41, line 4, in particular). The reference targeting ligand moiety, i.e. FK506, FK520, cyclosporine A, a steroid, etc, are capable of binding to or oligomerized with its receptor domain with high affinity (see page 35, line 19-22, page 35 through page 36, lines 1-10, in particular). The WO 95/02684 publication teaches other ligands which can be used for targeting i.e., steroids such as estrogen to binds to intracellular steroid receptor, i.e. estrogen receptor (see page 36, line 31-35, in particular) or drugs, i.e., FK506, cyclosporine that are known to bind to a particular intracellular receptor with high affinity, i.e., FKBP receptor and cyclophilin, respectively (see page 36, lines 36-37, page 40, lines 25-31, in particular). The WO 95/02684 publication teaches cyclosporine A (CsA) binds with high affinity (6nM) to its intracellular receptor cyclophilin as the targeting moiety in the reference chimeric molecule (see page 40, line 25-27, in particular). The publication also teaches the use of the FKBP such as FKBP12, which is an enzyme and also function as a receptor for peptidyl-prolyl isomerase ligand FK506, as the targeting moiety in a bifunctional molecule or fusion protein comprising FKBP that linked to Fas (see page 14, lines 1-6, in particular) and method of making the same as a pharmaceutical for mammalian host such as human (see page 10, line 22-23, in

particular). The targeting moiety can be fused to Fas protein without a linker via amide bond or via a linking group such as aliphatic chain of from about 12 to 24 carbon atoms (see page 37, line 5-23 through page 38, lines 1-6, in particular). The significant advantages of the reference ligand binding pair as targeting moiety are that the binding pair such as FK506 ligand unit binds to the receptor FKBP with high affinity such as a Kd $\leq 10^{-8}$ M (see page 33, line 33-35, in particular), preferably below about 10^{-7}, 10^{-9} or 10^{-10} (see page 35, lines 30-34, in particular), and thereby localizes the concentration of the therapeutic product (see page 44, lines 2-10, in particular). The reference bifunctional molecule of fusion protein has a molecule weight that does not exceed about 5000 daltons (5 kD) (see page 4, line 12, claim 18 of WO 95/02684 publication, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the estrogen targeting moiety that linked to a drug as taught by Forsgren et al for any one of the binding pair as a targeting moiety such as peptidyl-prolyl isomerase ligand, i.e. FK506, rapamycin or derivative thereof that binds to intracellular distributed receptor FKBP or cyclosporine that binds to intracellular distributed cyclophilin receptor as taught by the WO 95/02684 publication for a method for directing the biodistribution of a drug as taught by Forsgren et al to the intracellular distributed receptor as taught by WO 95/02684 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to substitute because the significant advantages of the reference ligand binding pair are that the ligand unit, i.e. FK506, rapamycin or derivative thereof or cyclosporine binds to the respective receptor, i.e. FKBP, cyclophilin with high affinity such as a Kd $\leq 10^{-8}$ M and localizes the concentration of the therapeutic product (see page 44, lines 2-10, in particular) as taught by the WO95/02684 publication (see page 33, line 33-35, in particular). Given the high binding affinity of the ligand receptor binding pair and the small size of the ligand as taught by the WO 95/02684 publication, any drug that fused to or linked to any peptidyl-prolyl isomerase ligand would obviously direct the distribution of said drug to the intracellular distributed peptidyl-prolyl isomerase receptor compared with free drug control (drug not linked or fused to peptidyl-prolyl isomerase ligand). The use of the peptidyl-prolyl isomerase ligand rather than the receptor FKBP in the high affinity binding pair as targeting molecule is within the purview of one ordinary skill in the art since any

peptidyl-prolyl isomerase ligand such as FK506, rapamycin and derivative thereof bind to intracellular receptor FKBP with high affinity while cyclosporine A interacts with its intracellular receptor cyclophilin as taught by the WO 95/2684 publication (page 40 lines 25-29). The concept is analogous to the use of small steroid such as estrogen that binds to the intracellular estrogen receptor as taught by WO 95/2684 publication or the estradiol-17 beta phosphate that linked to drug that binds to intracellular modulating protein such as soluble estramustine in the ventral prostate with high affinity as taught by Forsgren et al.

(10) Response to Argument

Claim Rejection - 35 USC § 103 (a)

At pages 11-12 of the Brief, Appellants submitted that the Examiner's position is based on the incorrect reading of the recombinant protein of WO 95/02684. Specifically, Examiner's position is based on the incorrect assumption that the recombinant proteins include peptidyl-prolyl isomerase ligands. In particular, the Appellants stress that WO 95/02684 teaches a system that includes two elements: (1) chimeric proteins and (2) ligand molecules capable of oligomerizing the chimeric proteins. According to the cited reference, the chimeric protein includes a ligand-binding (or "receptor") domain fused to an action domain capable of initiating apoptosis (see page 3, lines 24-26). The cited reference further teaches that the receptor domain of such chimeric proteins are "capable of binding to FK-506-type ligand, a cyclosporine A-type ligand, tetracycline or a steroid ligand" that are present in a cell and are referred to in the cited reference as oligomerization ligands (see page 4, lines 31-35, emphasis added). Therefore, the cited reference does not teach a moiety such as a peptidyl-prolyl isomerase ligand FK506 type ligand, cyclosporine and rapamycin as a targeting domain of a chimeric molecule, but instead teaches that such molecules can be targeted, thereby inducing oligomerization in the cell. In other words, the reference refers to receptors such as FK506, and does not use ligands to those receptors for constructing bifunctional molecules (ligand plus drug) as claimed. Therefore, substitution of the targeting moiety, as taught in WO 95/02684, with the targeting moiety of Forsgren et al., would not result in the claimed bifunctional molecule of the present invention.

Appellant' arguments filed 6/23/06 have been fully considered but are not found persuasive. It is noted that the scope of the independent claims 16, 24 and 30 merely require any

peptidyl-prolyl isomerase ligand that linked to a drug as a bifunctional molecule having a molecular weight that does not exceed about 5000 daltons for a method for directing the distribution of said drug to any intracellular space. The claims do not recite the particular peptidyl-prolyl isomerase "ligand" as the targeting moiety in the bifunctional molecule as long as it binds to intracellular distributed protein. The WO 95/02684 publication teaches various peptidyl-prolyl isomerase ligand binding pairs such as FK506, FK520, rapamycin and derivative thereof that bind to an intracellular FKBP receptor, or estrogen that binds to estrogen receptor for targeting gene (see page 33, lines 25-27, page 36, lines 1-10, page 41, line 4, in particular).

In contrast to appellants' assertion that the WO95/02684 publication does not teach cyclosporine A as the targeting domain, the WO 95/02684 publication teaches cyclosporine A (CsA) binds with high affinity (6nM) to its intracellular receptor cyclophilin as the targeting moiety in the reference chimeric molecule (see page 40, line 25-27, in particular). The reference teaches ligand moiety, i.e. FK506, FK520, cyclosporine A, a steroid, etc, are capable of binding to or oligomerized with its intracellular receptor domain with high affinity (see page 35, line 19-22, page 35 through page 36, lines 1-10, in particular). The WO 95/02684 publication teaches other ligands which can be used for targeting i.e., steroids such as estrogen (see page 36, line 31-35, in particular) or drugs, i.e., FK506, cyclosporine that are known to bind to a particular intracellular receptor with high affinity, i.e., FKBP receptor, cyclophilin, respectively (see page 36, lines 36-37, page 40, lines 25-31, in particular). The WO 95/02684 publication teaches that the significant advantage of the reference ligand binding pair is that the ligand unit binds to the receptor with high affinity such as a Kd $\leq 10^{-8}$ M (see reference page 33, line 33-35, in particular), preferably below about 10^{-7}, 10^{-9} or 10^{-10} (see reference page 35, lines 30-34, in particular). In fact, the specification at page 21, lines 5-28 discloses the targeting moiety peptidyl-prolyl isomerase ligand, e.g. FK506, rapamycin, cyclosporine A, steroid hormone receptor ligands such as estrogen bind to intracellular biodistribution modulating proteins such as FKBP, cyclophilin and estrogen respective receptor, respectively (see specification, page 18, lines 24-31, page 19, lines 1-21, page 21, line 3-9, in particular). The specification discloses that the ligand should specifically bind to FKBP and has an affinity for the FKBP that is between about 10^{-6} and 10^{-10} (see specification page 21, lines 20-22, in particular). Therefore, substitution of the estrogen targeting moiety as taught by Forsgren et al., for the targeting moiety such as peptidyl-prolyl isomerase ligand i.e. FK506, rapamycin or cyclosporine A as taught by the WO95/02684 publication would result in the claimed bifunctional molecule of the present invention.

At page 13 of the Brief, Appellants submitted that the cited WO95/02684 reference teaches the concept for the inducible protein association is illustrated in Figure 12. The cited reference teaches the use of peptidyl-prolyl isomerase a receptor domain of the chimeric protein and liqands of peptidvl-prolyl isomerase as inducing oligomerized complexes. The Examiner also asserts in the Final Office Action the following: "WO 95/02684 publication teaches a bifunctional molecule such as fusion protein comprising a targeting moiety such as various peptidvl-prolyl isomerase ligand and linked to FAS (see page 14, lines 1-6, in particular) and methods of making the same as a pharmaceutical." However, the Appellants respectfully disagree. The cited passage discloses a chimeric protein comprising FAS linked to the targeting moiety FKBP12. FKBP12 is a peptidvl-prolyl isomerase - not the ligand of a peptidvl-prolyl isomerase.

Appellant' arguments filed 6/23/06 have been fully considered but are not found persuasive. As discussed supra, the scope of the independent claims 16, 24 and 30 merely require any peptidyl-prolyl isomerase ligand that linked to a drug as a bifunctional molecule having a molecular weight that does not exceed about 5000 daltons for a method for directing the distribution of said drug to any intracellular space. The claims do not recite the particular peptidyl-prolyl isomerase "ligand" as the targeting moiety in the bifunctional molecule as long as it binds to intracellular distributed protein. In addition to the use of the FKBP12, which is a receptor for FK506 (a peptidyl-prolyl isomerase ligand), as the targeting domain as one particular embodiment as taught by the WO 95/02684 publication, the WO 95/02684 publication teaches other embodiments such as the use of various peptidyl-prolyl isomerase ligand binding pairs such as FK506, FK520, rapamycin and derivative thereof that bind to an intracellular FKBP receptor, or estrogen that binds to estrogen receptor for targeting gene (see page 33, lines 25-27, page 36, lines 1-10, page 41, line 4, in particular). The WO 95/02684 publication teaches cyclosporine A (CsA), a cyclophilin ligand, binds with high affinity (6nM) to its intracellular receptor cyclophilin (see page 40, line 25-27, in particular). The WO 95/02684 publication teaches other ligands which can be used for targeting i.e., steroids such as estrogen (see page 36, line 31-35, in particular) or drugs, i.e., FK506, cyclosporine that are known to bind to a particular intracellular receptor with high affinity, i.e., FKBP receptor, cyclophilin, respectively (see page 36, lines 36-37, page 40, lines 25-31, in particular).

At page 14 of the Brief, Appellants submitted that the disclosure of FK506, cyclosporine and rapamycin in WO 95/02684 is within the context of their use as oligomerizing ligands; not as targeting domains of bifunctional molecules. The reference passage at page 4, lines 31-35 specifically states: As discussed in greater detail later, and by way of example, in various embodiments of this invention the chimeric protein is capable of binding to an FK506-ligand, a cyclosporine A-type ligand, tetracycline or a steroid ligand. Accordingly, the Appellants maintain that the cited reference does not teach use of ligands of peptidyl-prolyl isomerases as targeting moieties. If, in arguendo, one were to combine the teaching of WO 95/02684 with that of Forsgren et al., the result would be a bifunctional molecule having a drug moiety and a targeting moiety that is a peptidyl-prolyl isomerase, such as FBKP12. In contrast, the pending claims are directed to a bifunctional molecule having a drug moiety and a targeting moiety that is a ligand of a peptidyl-prolyl isomerase.

Appellant' arguments filed 6/23/06 have been fully considered but are not found persuasive. As noted above, appellants' argument appears to fixate on one particular embodiment of the WO 95/02684 publication teachings rather than the general concept of targeting using the reference high affinity ligand binding pairs, such as FK506, rapamycin and derivative thereof that are known to bind to intracellular receptor FBKP with high affinity such as a $Kd \leq 10^{-8}$ M (see reference page 33, line 33-35, in particular), preferably below about 10^{-7}, 10^{-9} or 10^{-10} (see reference page 35, lines 30-34, in particular) or cyclosporine that binds with high affinity (6nM) to its intracellular receptor cyclophilin as taught by the WO95/02684 (see page 40, line 25-27, in particular). Given the advantage of high affinity of binding among the binding pairs as taught by WO 95/02684, one of ordinary skill in the art at the time the invention was made would have had an expectation of success that any drug linked to any one of the ligand in such binding pair would obviously direct the distribution of such drug to the intracellular receptors and result in a modulated biodistribution of the drug in bifunctional molecule compared with the free drug alone.

At pages 15-16 of the brief, Appellants submitted that the disclosure of the cited reference WO 95/02684 publication is directed to use of (1) the chimeric proteins and (2) the ligand molecules capable of oligomerizing the chimeric proteins to induce apoptosis of the recipient cells. The cited reference does not teach use of the receptor domains as targeting moieties. In fact, in the context of the disclosure of WO95/02684, the chimeric proteins and the ligand molecules are both administered to the cells at the same time. Therefore, there is no

"targeting" mediated by the receptor domain of the chimeric protein as incorrectly asserted by the Examiner. As noted above, the claims of the present application require that upon administration to the host, the bifunctional molecule be directed to an intracellular space and results in a directed biodistribution of the drug as compared to a free drug control.

Appellant' arguments filed 6/23/06 have been fully considered but are not found persuasive. As noted above, appellants' argument appears to fixate on one particular embodiment of the WO 95/02684 teachings rather than the general concept of targeting using the reference high affinity ligand binding pairs, such as FK506, rapamycin and derivative thereof that are known to bind to intracellular receptor FBKP with high affinity such as a Kd $\leq 10^{-8}$ M (see reference page 33, line 33-35, in particular), preferably below about 10^{-7}, 10^{-9} or 10^{-10} (see reference page 35, lines 30-34, in particular) or cyclosporine that binds with high affinity (6nM) to its intracellular receptor cyclophilin as taught by the WO95/02684 publication (see page 40, line 25-27, in particular).

In contrast to appellants' assertion that there is no "targeting" mediated by the receptor domain of the chimeric protein, the WO 95/02684 publication teaches targeting gene (see page 41, line 4, in particular) using various high affinity ligand-receptor binding pairs discussed above. The WO 95/02684 teaches chimeric protein comprises at least one receptor domain capable of binding to a selected oligomerization ligand; the receptor domain is fused to an action domain capable-upon exposure to the ligand, initiating intracellular signal (see page 10, lines 8-13, in particular). The chimeric protein may further comprise an intracellular targeting domain capable of directing the chimeric protein to a desired cellular compartment (see page 4, lines 24-26, in particular). Given the *high affinity* of the ligand-receptor binding pairs as taught by the WO 95/02684 publication, the ligand in bifunctional molecule obviously directed biodistribution of the drug to the respective intracellular receptors and result in a modulated biodistribution of the bifunctional molecule upon administration in a host compared with the drug alone.

Finally, Forsgren et al teach a bifunctional molecule such as Estracyt which consisting of a drug moiety such as nitrogen mustard linked to a targeting moiety such as estradiol-17 beta phosphate wherein said targeting moiety has affinity for its intracellular biodistribution modulating protein such as soluble estramustine located in the ventral prostate (see abstract, page 5158, col. 1, page 5161, col. 2, in particular).

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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September 1, 2006

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